25. The pharmaceutical kit according to claim 21 wherein the opioid antagnoist is naltrexone present in the amount of 10-25 mg, and the antidepressant is fluoxetine present in the amount less than 20 mg.

REMARKS

By the present amendment, new claims 8-25 have been introduced in order to provoke an interference with U.S. Patent 5,958,962.

I. NEW CLAIMS 8-21

Support for the newly added claims can be found throughout the application. For example, descriptive support for a method of treating alcoholism together with depression, as recited in Claim 8, can be found at least in Example 4 of the patent. See, e.g., column 6, lines 59-60.

Example 1 appearing in column 5 provides descriptive support for providing separate treatments of the antagonist and depressant. See, e.g., column 5, lines 61-63. Accordingly, this example provides adequate written descriptive support for a "kit" claim such as that of new claims 21-25.

The use of naltrexone as well as the claimed amount of 10-150 mg/day is found at column 3, lines 14-17 and 34-36. As to the use of naltrexone in an amount of 10-25 mg/day, attention is directed towards the disclosure at column 4, lines 37-44, as well as claims 3 and 4 of the patent.

Support for the use of fluoxetine as the antidepressant can be found at least at column 5, line 12 of the specification. Moreover, descriptive support for the claimed amounts of fluoxetine can be

found at least in column 2, lines 4-9 and column 3, lines 25-33 which incorporates portions of the Physician Desk Reference (PDR) by reference. A copy of the PDR disclosure relating to fluoxetine is being filed concurrently herewith.

In looking at the PDR disclosure concerning fluoxetine, attention is directed toward the "Description" section appearing on page 943, and the "Dosage And Administration" and "How Supplied" sections appearing on page 947 of the PDR. In particular, the "Depression" subsection of the "Dosage And Administration" section sets forth a maximum recommended dosage of 80 mg, as well as a recommended dosage of 20-80 mg. It further discloses that doses greater than 20 mg may be given twice a day, corresponding to 10-40 mg dosages. Finally, the fourth paragraph of the "Depression" subsection states that a "lower" dosage should also be considered for patients on "multiple medications."

Accordingly, the PDR, which is incorporated by reference into the Dante patent, provides descriptive support for all of the numerical recitations involving fluoxetine in claims 8-25.

No new matter has been introduced by these new claims.

II. REQUEST FOR INTERFERENCE

In accordance with the provisions of 37 C.F.R. § 1.607, Applicants also request that an interference be declared between this reissue application and unexpired U.S. Patent 5,958,962.

In accordance with the provisions of 37 C.F.R. §1.607(a), Applicants offer the following:

(1) The patent in question is U.S. Patent 5,958,962 which issued September 28, 1999;

(2) The proposed count is as follows:

Claims 1, 2 or 3 of U.S. Patent 5,958,962

or Claim 1, 8, 14 or 21 of this reissue application;

(3) Each of claims 1-3 of U.S. Patent 5,958,962 correspond to the proposed count;

(4) Each of claim 1-25 of this reissue application correspond to the proposed count.

As to 37 C.F.R. §1.608, the effective filing date of the present reissue application, March 2, 1993, is **<u>more than 18 months earlier</u>** than the effective filing date of U.S. Patent 5,958,962, September 19, 1994. Accordingly, it is submitted that **<u>no</u>** showing under 37 C.F.R. §1.608 is required.

An early declaration of interference is in order and such action is earnestly solicited.

As a final matter, should the examiner have any questions regarding this paper, or the reissue application in general, he/she is invited to telephone the undersigned at his/her earliest convenience.

Respectfully submitted,

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<u>CERTIFICATE OF EXPRESS MAILING UNDER 37 C.F.R. §1.10</u>

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail, No. EL403201815US in an envelope addressed to: Assistant Commissioner for Patents, BOX REISSUE APPLICATION, Washington, D.C. 20231, on this 28th day of September, 2000.

Everardo McFarlane

9-28-00
Date

1995 PDR same as 1993 PDR for Prozac

...ible complications of sudden steroid ...

...ancy—Safe use of Nalfon during pregnancy ...s not been established; therefore, adminis... ...ant patients and nursing mothers is not ... ...Reproduction studies have been performed in ... When fenoprofen was given to rats during ...ntinued until the time of labor, parturition ...similar results have been found with other ...ti-inflammatory drugs that inhibit prosta...

...ren—Fenoprofen calcium is not recom... ...in children because documented clinical ex... ...en insufficient to establish safety and a suit... ...men in the pediatric age group.

...EACTIONS

...studies for rheumatoid arthritis, osteoarthri... ...moderate pain and studies of pharmacokinet... ...were compiled from a checklist of potential ...ons, and the following data emerged. These ...ervations in 6,786 patients, including 188 ob... ...least 52 weeks. For comparison, data are also ...on complaints received from the 266 patients ...placebo in these same trials. During short-term ...algesia, the incidence of adverse reactions was ...er than that seen in longer-term studies.

...GREATER THAN 1%

...al Relationship

...—During clinical trials with Nalfon® ...Calcium, USP), the most common adverse reac... ...trointestinal in nature and occurred in 20.8% ...receiving Nalfon as compared to 16.9% of pa... ...placebo. In descending order of frequency, ...included dyspepsia (10.3%, Nalfon, vs 2.3%, ...(7.1% vs 7.1%), constipation (7% vs 1.5%), ...% vs 1.9%), abdominal pain (2% vs 1.1%), and ... vs 4.1%).

...discontinued because of adverse gastrointesti... ...in less than 2% of patients during premarket...

...—The most frequent adverse neurologic ...headache (8.7% treated vs 7.5% placebo) and ...% vs 6.4%). Dizziness (6.5% vs 5.6%), tremor ..., and confusion (1.4% vs none) were noted less ...

...discontinued in less than 0.5% of patients be... ...side effects during premarketing studies. ...—Increased sweating (4.6% vs 0.4%), ... vs 0.8%), and rash (3.7% vs 0.4%) were re...

...discontinued in about 1% of patients because of ...effect related to the skin during premarketing ...

...—Tinnitus (4.5% vs 0.4%), blurred vision ..., and decreased hearing (1.6% vs none) were ...

...discontinued in less than 0.5% of patients be... ...effects related to the special senses during ...studies.

...—Palpitations (2.5% vs 0.4%).

...discontinued in about 0.5% of patients because ...cardiovascular reactions during premarketing ...

...—Nervousness (5.7% vs 1.5%), asthenia (5.4% ...peripheral edema (5.0% vs 0.4%), dyspnea (2.8% vs ... (1.7% vs 1.5%), upper respiratory infection ... and nasopharyngitis (1.2% vs none).

...LESS THAN 1%

...al Relationship

...adverse reactions, occurring in less than 1% of ...were reported in controlled clinical trials and vol... ...made since Nalfon® (Fenoprofen Calcium; ...initially marketed. The probability of a causal ...exists between Nalfon and these adverse reac...

...—Gastritis, peptic ulcer with/without per... ...intestinal hemorrhage, anorexia, flatulence, ...and blood in the stool. Increases in alkaline phos... and SGOT, jaundice, and cholestatic hepatitis ...(see Precautions).

...Tract—Dysuria, cystitis, hematuria, oliguria, ...interstitial nephritis, nephrosis, and papil... (see Warnings).

...—Angioedema (angioneurotic edema).

...—Purpura, bruising, hemorrhage, thrombocy... ...anemia, aplastic anemia, agranulocyto... ...penia.

...—Anaphylaxis, urticaria, malaise, insomnia, ...

...LESS THAN 1%

...ability Unknown

...reported either in clinical trials or spontane... ...in circumstances in which a causal relation... ...be established. However, with these rarely ...ctions, the possibility of such a relationship can... not ...luded. Therefore, these observations are listed to ale... ...physician.

Skin and Appendages—Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, and alopecia.

Digestive System—Aphthous ulcerations of the buccal mucosa, metallic taste, and pancreatitis.

Cardiovascular—Atrial fibrillation, pulmonary edema, electrocardiographic changes, and supraventricular tachycardia.

Nervous System—Depression, disorientation, seizures, and trigeminal neuralgia.

Special Senses—Burning tongue, diplopia, and optic neuritis.

Miscellaneous—Personality change, lymphadenopathy, mastodynia, and fever.

OVERDOSAGE

Signs and Symptoms—Symptoms of overdose appear within several hours and generally involve the gastrointestinal and central nervous systems. They include dyspepsia, nausea, vomiting, abdominal pain, dizziness, headache, ataxia, tinnitus, tremor, drowsiness, and confusion. Hyperpyrexia, tachycardia, hypotension, and acute renal failure may occur rarely following overdose. Respiratory depression and metabolic acidosis have also been reported following overdose with certain NSAIDs.

Treatment—To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Alkalinization of the urine, forced diuresis, peritoneal dialysis, hemodialysis, and charcoal hemoperfusion do not enhance systemic drug elimination.

DOSAGE AND ADMINISTRATION

Analgesia—For the treatment of mild to moderate pain, the recommended dosage is 200 mg every 4 to 6 hours, as needed.

Rheumatoid Arthritis and Osteoarthritis—The suggested dosage is 300 to 600 mg, 3 or 4 times a day. The dose should be tailored to the needs of the patient and may be increased or decreased depending on the severity of the symptoms. Dosage adjustments may be made after initiation of drug therapy or during exacerbations of the disease. Total daily dosage should not exceed 3,200 mg.

If gastrointestinal complaints occur, Nalfon® (Fenoprofen Calcium, USP) may be administered with meals or with milk. Although the total amount absorbed is not affected, peak blood levels are delayed and diminished.

Patients with rheumatoid arthritis generally seem to require larger doses of Nalfon than do those with osteoarthritis. The smallest dose that yields acceptable control should be employed.

Although improvement may be seen in a few days in many patients, an additional 2 to 3 weeks may be required to gauge the full benefits of therapy.

HOW SUPPLIED

(℞) Pulvules:

200 mg* (white and ocher) (No. 415)—(Identi-Code† H76) (RxPak‡ of 100) NDC 0777-0876-02

300 mg* (yellow and ocher) (No. 416)—(Identi-Code† H77) (RxPak‡ of 100) NDC 0777-0877-02; (500s) NDC 0777-0877-03

(℞) Tablets (DISTA imprinted on one side, NALFON on other side):

600 mg* (yellow, paracapsule-shaped, scored) (No. 1900)—(RxPak‡ of 100) NDC 0777-2159-02; (500s) NDC 0777-2159-03

* Equivalent to fenoprofen.

† Identi-Code® (formula identification code, Dista).

‡ All RxPaks (prescription packages, Dista) have safey closures.

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

[121390]

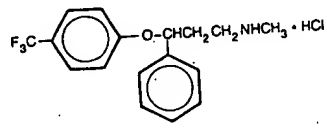
PROZ...®

[prō ...

(fluo... ...ydrochloride)

DESCRIPTION

Prozac® (Fluoxetine Hydrochloride) is an antidepressant for oral administration; it is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO \cdot HCl$. Its molecular weight is 345.79. The structural formula is:



Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

Each Pulvule® contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol) or 20 mg (64.7 μmol) of fluoxetine. The Pulvules also contain F D & C Blue No. 1, gelatin, iron oxide, silicone, starch, titanium dioxide, and other inactive ingredients.

The oral solution contains fluoxetine hydrochloride equivalent to 20 mg/5 mL (64.7 μmol) of fluoxetine. It also contains alcohol 0.23%, benzoic acid, flavoring agent, glycerin, purified water, and sucrose.

CLINICAL PHARMACOLOGY

Pharmacodynamics—The antidepressant and antiobsessive-compulsive action of fluoxetine is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Antagonism of muscarinic, histaminergic, and α_1-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs.

Absorption, Distribution, Metabolism, and Excretion:

Systemic Bioavailability—In man, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours.

The Pulvule and oral solution dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, fluoxetine may be administered with or without food.

Protein Binding—Over the concentration range from 200 to 1,000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important (*see* Precautions).

Enantiomers—Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Metabolism—Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other, unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Related to Metabolism/Elimination—The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.

Variability in Metabolism—A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome PA450IID6. Such individuals are referred to as

Continued on next page

This product information was prepared in June 1994. Current information on these and other products of Dista Products Products Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.

Dista—Cont.

"poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-IID6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine's metabolism, like that of a number of other compounds including tricyclic and other selective serotonin antidepressants, involves the P450IID6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the tricyclic antidepressants) may lead to drug interactions (*see* Drug Interactions *under* Precautions).

Accumulation and Slow Elimination—The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/ day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady state levels after prolonged dosing are similar to levels seen at 4–5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of Prozac® (Fluoxetine Hydrochloride).

Liver Disease—As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared to the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared to the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used (*see* Precautions *and* Dosage and Administration).

Renal Disease—In single dose studies, the pharmacokinetics of fluoxetine and norfluoxetine were similar among subjects with all levels of impaired renal function including anephric patients on chronic hemodialysis. However, with chronic administration, additional accumulation of fluoxetine or its metabolites (possibly including some not yet identified) may occur in patients with severely impaired renal function and use of a lower or less frequent dose is advised (*see* Precautions).

Age—The disposition of single doses of fluoxetine in healthy elderly subjects (greater than 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥ 60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Clinical Trials:

Depression—The efficacy of Prozac for the treatment of patients with depression (≥ 18 years of age) has been studied in 5- and 6-week placebo-controlled trials. Prozac was shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). Prozac was also significantly more effective than placebo on the HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subfactor.

Two 6-week controlled studies comparing Prozac, 20 mg, and placebo have shown Prozac, 20 mg daily, to be effective in the treatment of elderly patients (≥ 60 years of age) with depression. In these studies, Prozac produced a significantly higher rate of response and remission as defined respectively by a 50% decrease in the HAM-D score and a total endpoint HAM-D score of ≤ 7. Prozac was well tolerated and the rate of treatment discontinuations due to adverse events did not differ between Prozac (12%) and placebo (9%).

Obsessive Compulsive Disorder.—The effectiveness of Prozac for the treatment for obsessive compulsive disorder (OCD) was demonstrated in two 13-week, multicenter, parallel group studies (Studies 1 and 2) of adult outpatients who received fixed Prozac doses of 20, 40, or 60 mg/day (on a once a day schedule, in the morning) or placebo. Patients in both studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS, total score) ranging from 22 to 26. In Study 1, patients receiving Prozac experienced mean reductions of approximately 4 to 6 units on the YBOCS total score, compared to a 1-unit reduction for placebo patients. In Study 2, patients receiving Prozac experienced mean reductions of approximately 4 to 9 units on the YBOCS total score, compared to a 1-unit reduction for placebo patients. While there was no indication of a dose response relationship for effectiveness in Study 1, a dose response relationship was observed in Study 2, with numerically better responses in the 2 higher dose groups. The following table provides the outcome classification by treatment group on the CGI improvement scale for studies 1 and 2 combined.

Outcome Classification (%) on CGI Improvement Scale for Completers in Pool of Two OCD Studies

Classification	Placebo	Prozac		
		20 mg	40 mg	60 mg
Worse	8%	0%	0%	0%
No Change	64%	41%	33%	29%
Minimally Improved	17%	23%	28%	24%
Much Improved	8%	28%	27%	28%
Very Much Improved	3%	8%	12%	19%

Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

INDICATIONS AND USAGE

Depression—Prozac® (Fluoxetine Hydrochloride) is indicated for the treatment of depression. The efficacy of Prozac was established in 5- and 6-week trials with depressed outpatients (≥ 18 years of age) whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (*see* Clinical Trials *under* Clinical Pharmacology).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of Prozac in hospitalized depressed patients has not been adequately studied.

The effectiveness of Prozac in long-term use, that is, for more than 5 to 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Obsessive-Compulsive Disorder—Prozac is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R.–; ie, the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Prozac was established in 13-week trials with obsessive-compulsive outpatients whose diagnoses corresponded most closely to the DSM-III-R category of obsessive-compulsive disorder (*see* Clinical Trials *under* Clinical Pharmacology).

Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of Prozac in long-term use, ie, for more than 13 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* Dosage and Administration).

CONTRAINDICATIONS

Prozac® (Fluoxetine Hydrochloride) is contraindicated in patients known to be hypersensitive to it.

Monoamine Oxidase Inhibitors—There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, Prozac should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses [*see* Accumulation and Slow Elimination *under* Clinical Pharmacology]) should be allowed after stopping Prozac before starting an MAOI.

WARNINGS

Rash and Possibly Allergic Events—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In premarketing clinical trials, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac should be discontinued.

PRECAUTIONS

General—Anxiety and Insomnia—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac® (Fluoxetine Hydrochloride). These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

In controlled clinical trials for obsessive-compulsive disorder, insomnia was reported in 30% of patients treated with Prozac and in 22% of patients treated with placebo. Anxiety was reported in 14% of patients treated with Prozac and in 7% of patients treated with placebo. These 2 symptoms led to drug discontinuation in 2% of patients treated with Prozac and no patients treated with placebo.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo and 3% of patients treated with tricyclics. However, only rarely have patients discontinued treatment with Prozac because of weight loss.

In controlled clinical trials for OCD, 17% of patients treated with Prozac and 10% of patients treated with placebo reported anorexia. One patient discontinued treatment with Prozac because of anorexia.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1%

of fluoxetine treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Mania/hypomania was reported in 1% of patients treated with fluoxetine in controlled clinical OCD trials.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

In controlled clinical trials for OCD, 1 patient treated with fluoxetine experienced a seizure.

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* Clinical Pharmacology *and* Dosage and Administration).

Use in Patients With Concomitant Illness—Clinical experience with Prozac® (Fluoxetine Hydrochloride) in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with Prozac is instituted or discontinued.

Interference With Cognitive and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients —Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests —There are no specific laboratory tests recommended.

Drug Interactions —As with all drugs, the potential for interaction by a variety of mechanisms (eg, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Drugs Metabolized by P450IID6—Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme P450IID6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. Many drugs, such most antidepressants including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite the sum of the plasma concentrations of the 4 active enantiomers is comparable between poor and extensive metabolizers (*see* Variability in Metabolism *under* Clinical Pharmacology).

Fluoxetine, like other agents that are metabolized by P450IID6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble "poor metabolizers." Therapy with medications that are predominantly metabolized by the P450IID6 system and that have a relatively narrow therapeutic index (*see* list below), should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or have taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of "poor metabolizers." If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by P450IID6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (eg, flecainide, vinblastine, carbamazepine, and tricyclic antidepressants).

Tryptophan—Five patients receiving Prozac® (Fluoxetine Hydrochloride) in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors—*See* Contraindications.

Other Antidepressants—There have been greater than 2-fold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Lithium—There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Diazepam Clearance—The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Phenytoin—Patients on stable doses of phenytoin have developed elevated plasma phenytoin concentrations and clinical phenytoin toxicity following initiation of concomitant fluoxetine treatment.

Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

CNS Active Drugs—The risk of using Prozac in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Electroconvulsive Therapy—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility —There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for 2 years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately 5 and 9 times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy —Teratogenic Effects —Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses 9 and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac® (Fluoxetine Hydrochloride). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery —The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers —Because Prozac is excreted in human milk, nursing while on Proazc is not recommended. In 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on Prozac developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 240 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding.

Usage in Children —Safety and effectiveness in children have not been established.

Usage in the Elderly —Evaluation of patients over the age of 60 who received Prozac 20 mg daily revealed no unusual pattern of adverse events relative to the clinical experience in younger patients. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs. (*see* Age *under* Clinical Pharmacology).

Hyponatremia —Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In a placebo-controlled, double-blind trial, 10 of 313 fluoxetine patients and 6 of 320 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

Platelet Function —There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

ADVERSE REACTIONS

Commonly Observed —The most commonly observed adverse events associated with the use of Prozac® (Fluoxetine Hydrochloride) and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

In controlled clinical trials for OCD using fixed doses of 20, 40, or 60 mg daily, adverse events observed at an incidence of at least 5% for Prozac and for which the incidence was approximately twice or more the incidence among placebo-treated patients included: somnolence, anxiety, tremor, nausea, dyspepsia, gastrointestinal disorder, vasodilatation, dry mouth, sweating, rash, abnormal vision, yawn, decreased libido, and abnormal ejaculation.

Associated With Discontinuation of Treatment —Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

In controlled clinical trials for OCD, 12% of patients treated with Prozac discontinued treatment due to adverse events. The most common events were anxiety (2%) and rash/urticaria (2%).

Incidence in Controlled Clinical Trials —

Depression—Table 1 enumerates adverse events that occurred at a frequency of 1% or more among patients treated with Prozac who participated in controlled trials comparing Prozac with placebo.

Obsessive-Compulsive Disorder—Table 2 enumerates adverse events that occurred at a frequency of 2% or more among patients on Prozac who participated in controlled trials comparing Prozac with placebo in the treatment of OCD.

The prescriber should be aware that the figures in Tables 1 and 2 cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in

Continued on next page

This product information was prepared in June 1994. Current information on these and other products of Dista Products Products Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.

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the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

[See Table 1 below.]
[See Table 2 on next page.]

Other Events Observed During Premarketing Evaluation of Prozac® (Fluoxetine Hydrochloride)—During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (ie, reduced) number of standardized event categories.

In the tabulations that follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited on at least 1 occasion while receiving Prozac. All reported events are included except those already listed in Table 1, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole—*Frequent:* chills; *Infrequent:* chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System—*Infrequent:* angina, pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; *Rare:* AV block first degree, bradycardia, bundle branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System—*Frequent:* increased appetite; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System—*Infrequent:* hypothyroidism; *Rare:* goiter and hyperthyroidism.

Hemic and Lymphatic System—*Infrequent:* anemia and lymphadenopathy; *Rare:* bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional—*Frequent:* weight loss; *Infrequent:* generalized edema, hypoglycemia, peripheral edema, and weight gain; *Rare:* dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal System—*Infrequent:* arthritis, bone pain, bursitis, tenosynovitis, and twitching; *Rare:* bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System—*Frequent:* abnormal dreams and agitation; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System—*Frequent:* bronchitis, rhinitis, and yawn; *Infrequent:* asthma, epistaxis, hiccup, hyperventilation, and pneumonia; *Rare:* apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages—*Infrequent:* acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; *Rare:* eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses—*Infrequent:* amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System—*Infrequent:* abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; *Rare:* abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postintroduction Reports—Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction, that are not listed above, and that may have no causal relationship with the drug include the following: aplastic anemia, cerebral vascular accident, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, hyperprolactinemia, immune-related hemolytic anemia, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, pancreatitis, pancytopenia, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, and violent behaviors.

TABLE 1—TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Preferred Term*	Percentage of Patients Reporting Event: Prozac (N = 1,730)	Placebo (N = 799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido decreased	1.6	—
Light-headedness	1.6	—
Concentration, decreased	1.5	—
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	—
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4
Body as a Whole		
Asthenia	4.4	1.9
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	—
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.0
Flu-like syndrome	2.8	1.9
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.6
Dyspnea	1.4	—
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	2.0	2.4
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful†	2.6	2.1
Sexual dysfunction	1.9	—
Impotence, sexual‡	1.7	0.4
Frequent micturition	1.6	—
Urinary tract infection	1.2	—
Special Senses		
Vision disturbance	2.8	1.8

* Events reported by at least 1% of patients treated with Prozac are included.
† Denominator used was females only (N = 1,210 Prozac; N = 523 placebo).
‡ Denominator used was males only (N = 520 Prozac; N = 276 placebo).
—Incidence less than 1%.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class—Prozac® (Fluoxetine Hydrochloride) is not a controlled substance.

Physical and Psychological Dependence—Prozac has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with Prozac did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Prozac (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience—As of December 1987, there were 2 deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L, respectively. A second death involved 3 drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced 2 grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (see Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the 2 deaths noted above, all other overdose cases recovered without residua.

Since introduction, reports of death attributed to overdose of fluoxetine alone have been extremely rare.

Animal Experience—Studies in animals do not provide precise or necessarily valid information about the treatment of human overdose. However, animal experiments can provide useful insights into possible treatment strategies.

The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg respectively. Acute high oral doses produced hyperirritability and convulsions in several animal species.

Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

In a separate single-dose study, the ECG in dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed. Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose (*see* Management of Overdose).

Management of Overdose—Establish and maintain an airway; ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose.

Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures. Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

There are no specific antidotes for Prozac® (Fluoxetine Hydrochloride).

Due to the large volume of distribution of Prozac, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

In managing overdosage, consider the possibility of multiple drug involvement. A specific caution involves patients taking or recently having taken fluoxetine who might ingest by accident or intent, excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* Other Antidepressants *under* Precautions).

The physician should consider contacting a poison control center on the treatment of any overdose. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*.

DOSAGE AND ADMINISTRATION

Depression:

Initial Treatment—In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 mg to 80 mg/day. Studies comparing fluoxetine 20, 40, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory antidepressant response. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose.

A dose increase may be considered after several weeks if no clinical improvement is observed. Doses above 20 mg/day may be administered on a once a day (morning) or b.i.d. schedule (ie, morning and noon) and should not exceed a maximum dose of 80 mg/day.

As with other antidepressants, the full antidepressant effect may be delayed until 4 weeks of treatment or longer.

As with many other medications, a lower or less frequent dosage should be used in patients with renal and/or hepatic impairment. A lower or less frequent dosage should also be considered for patients, such as the elderly (*see* Usage in the Elderly *under* Precautions), with concurrent disease or on multiple medications.

Maintenance/Continuation/Extended Treatment—There is no body of evidence available to answer the question of how long the patient treated with fluoxetine should remain on it. It is generally agreed among expert psychopharmacologists (circa 1987) that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Obsessive-Compulsive Disorder:

Initial Treatment—In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of obsessive-compulsive disorder, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo (*see* Clinical Trials *under* Clinical Pharmacology). In one of these studies, no dose response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once a day (ie, morning) or b.i.d. schedule (ie, morning and noon). A dose range of 20 to 60 mg/day is recommended, however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.

As with the use of Prozac in depression, a lower or less frequent dosage should be used in patients with renal and/or hepatic impairment. A lower or less frequent dosage should also be considered for patients, such as the elderly (*see* Usage in the Elderly *under* Precautions), with concurrent disease or on multiple medications.

Maintenance/Continuation Treatment—While there are no systematic studies that answer the question of how long to continue Prozac, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Prozac after 13 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.

HOW SUPPLIED

(℞) Pulvules: 10 mg* green and gray (No. 3104)—(100s) NDC 0777-3104-02

20 mg* green and off-white (No. 3105)—(100s) NDC 0777-3105-02; (ID†100)NDC 0777-3105-33

(℞) Liquid, Oral Solution: 20 mg*/5 mL, mint flavor (M-5120‡)—(120 mL) NDC 0777-5120-58

* Fluoxetine base equivalent.

† Identi-Dose® (unit dose medication, Dista).

‡ Dispense in a tight, light-resistant container.

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

Animal Toxicology: Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

[031494]

Shown in Product Identification Guide, page 309

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS FOR OBSESSIVE-COMPULSIVE DISORDER

Body System/ Preferred Team*	Percent of Patients Reporting Event Prozac (N=264)	Placebo (N=89)	Body System/ Preferred Team	Percent of Patients Reporting Event Prozac (N=264)	Placebo (N=89)
Nervous			**Body as a Whole**		
Insomnia	30	22	Headache	33	24
Somnolence	17	7	Asthenia	15	10
Anxiety	14	7	Flu syndrome	10	7
Dizziness	13	11	Pain	6	4
Libido, decreased	11	2	Injury, accidental	4	2
Tremor	9	1	Surgical procedure	3	—
Abnormal dreams	5	2	Chest pain	3	1
Thinking, abnormal	4	2	Allergic reaction	3	—
Sleep disorder	3	1	Fever	2	1
Confusion	2	1	**Respiratory**		
Myoclonus	2	—	Pharyngitis	11	9
Agitation	2	1	Yawn	7	—
Amnesia	2	1	Sinusitis	5	2
Digestive			Cough, increased	3	2
Nausea	27	13	**Cardiovascular**		
Diarrhea	18	13	Vasodilatation	5	—
Anorexia	17	10	Palpitations	2	1
Dry mouth	12	3	**Musculoskeletal**		
Dyspepsia	10	4	Myalgia	5	4
Gastrointestinal disorder	6	1	Arthralgia	3	2
Melena	2	—	**Urogenital**		
Skin and Appendages			Urinary freqeuncy	4	1
Sweating	7	—	Abnormal ejaculation†	7	—
Rash	6	3	**Hemic and Lymphatic**		
Pruritus	3	1	Lymphadenopathy	2	—
Acne	2	1	**Metabolic and Nutritional**		
			Weight loss	5	3
			Special Senses		
			Ambylopia	3	1
			Abnormal vision	2	—
			Taste perversion	2	1
			Tinnitus	2	—

* Events reported by at least 2% of patients treated with Prozac are included, except the following events which had an incidence on placebo ≥ Prozac: abdominal pain, back pain, constipation, depression, dysmenorrhea, flatulence, infection, menstrual disorder, nervousness, rhinitis, tooth disorder, and twitching.

† Denominator used was males only (N=116 Prozac; N=43 placebo).

— Adverse event not reported by placebo-treated patients.

[See table on next page.]

Continued on next page